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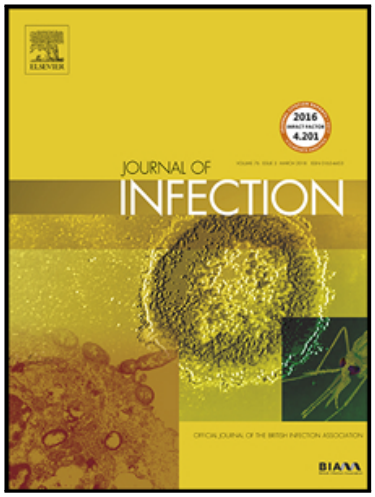

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Letter to the Editor

Who is a super-spreader? Determinants of people with higher PCR copy number of SARS-CoV-2 during Mar 2020 to June 2021 in Japan

Who is a super-spreader?

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Dear Editor,

In this Journal, Majra and colleagues reviewed the role of `super-spreaders' in the COVID-19 pandemic (1). Since the time of the SARS-CoV epidemic in 2003 and the MERS-CoV epidemic in

2012, it was found that not all patients were equally infectious; super-spreaders were highly contagious to their surroundings and could transmit the infection (2). Based on the experience of these two epidemics, a super-spreader can be defined as a patient who has a high viral load, sheds virus for a long period of time, and is not necessarily critically ill (3). In the Covid-19 pandemic, it has also been noted that high viral load leads to high infectivity (4) (5), and that the presence of super-spreaders is involved in super-spreading events, where some individuals spread to a disproportionate number of individuals, compared to most individuals who infected only a few or none (3) (6). It has also been reported that patients with severe disease have higher viral load and longer viral shedding period compared to patients with mild disease (7). However, few studies have examined the characteristics of people with high copy number, taking into account the fact that viral load changes over time. To that end, we conducted a single-center, retrospective study in patients diagnosed with COVID-19 and had their PCR copy number measured multiple times (Supplementary materials 1). Between March 2020 and June 2021, patients with a confirmed diagnosis of COVID-19, admitted to Tokyo Medical and Dental University, with polymerase chain reaction (PCR) copy number measured one or more times (median tested times: 2, range 1-26), were included in the study. A total of 379 patients were eligible for the study.

Table 1 shows the demographic data of the patients. The median age of the patients was 59 years, and about 33% were female. Median number of PCR tests was 2 (range: 1-26). In more than 90% of the patients who had more than one PCR test performed, the viral load was its maximum for that individual at the first or second test. About 59% had underlying disease and about 21% had more than three underlying diseases. Underlying diseases included hypertension (146, 38.5%), diabetes mellitus (82, 21.6%), dyslipidemia (70, 18.5%), hyperuricemia (29, 7.7%), rheumatoid arthritis (8, 2.1%), cancer (71, 18.7%), chronic kidney disease (25, 6.6%), stroke (19, 5.0%), heart disease (including myocardial infarction, atrial fibrillation, chronic heart disease, 34, 9.0%), and lung disease (including asthma and chronic obstructive lung disease, 41, 10.8%). All but one patient in this study were unvaccinated.

Table 2 shows the results of multivariate regression analysis between patient characteristics and log-transformed copy number. It was found that patients with diabetes mellitus, rheumatoid arthritis and history of stroke were significantly more likely to have a higher copy number of log of SARS-CoV-2 (coefficient: 1.25 (95% confidence interval (CI): 0.16-2.35), 3.22 (95% CI: 0.14-6.31), and 2.37 (95% CI: 0.34-4.41), respectively). Patients who had three or more underlying diseases were also significantly associated with increased copy number (coefficient: 1.83: (95% CI: 0.45-3.20)) than those without underlying diseases. After adjustment for gender, age, and smoking status, the associations with having three or more diseases, diabetes mellitus, rheumatoid arthritis, and stroke remained statistically significant (model 2). Detailed discussion is presented in Supplementary materials 2.

This study has several limitations. First, some of the patients included in the analysis were transferred from other hospitals, and it is possible that the copy number of the virus was modified by the treatment before the transfer. Second, the patients we analyzed were moderately to severely ill, and the association of viral load with underlying disease in patients with mild disease is not clear. Third, since the study period was between April 2020 and July 2021, few patients with the Delta variant carrying the L452R mutation were included. Hence, we do not know whether the difference in strains modified the association between the risk factors that were studied and the viral copy number.

There are several study strengths. First, we have conducted multiple PCR tests over time and have examined the association between possible risk factors and viral copy number using the maximum value, considering that viral load changes over time. Second, in our study, specimens for PCR testing were collected from the nasopharynx by a limited number of medical doctors, so the quality of the specimens was maintained. Third, the duration of the study was longer than one year and the number of patients included was larger than that of previous studies (8) (7) (9).

Clinical implications can be drawn as follows. First, in SARS-CoV-2 infections, it has been reported that infections could occur from super-spreaders who were highly contagious to their

surroundings. Thus, our finding will provide useful information for identifying super-spreaders using information on underlying diseases and laboratory data at the time of admission. For example, by identifying potential super-spreaders based on the information, physician could isolate patients in private rooms and elicit the attention of medical personnel to prevent nosocomial cluster outbreaks (10) (1) . Second, among patients who underwent multiple PCR tests, more than 90% had reached maximum viral load on the first or second test. This suggests that special infection control measures, such as isolation and alerting healthcare workers, need to be taken especially during the early stages, for patients who are thought to be at high risk of higher viral copy numbers based on the information on underlying diseases and laboratory data at the time of admission.

In moderately to severely ill COVID-19 hospitalized patients, diabetes mellitus, rheumatoid arthritis stroke, and a history of having three or more disease were associated with higher viral load, even after adjusting for age and gender. Lower platelet count and lower CRP levels on admission were also associated with higher viral load (Supplementary Table 1). Our study showed possible characteristics of super-spreaders. More research is needed to address the prevention of secondary infections caused by super-spreaders.

Authors' contributions:

Tomoki Kawahara: Software, Visualization, Writing-Original draft preparation.

Yutaka Ueki: Resources.

Nobutoshi Nawa: Writing-Review & Editing.

Shigeru Miyamae: Resources.

Mariko Hanafusa: Resources, Data curation.

Yuki Goto: Resources, Data curation.

Shuji Tohda: Resources.

Takeo Fujiwara: Conceptualization, Writing-Review & Editing, Supervision.

All the authors provided intellectual input and approved the final draft of the manuscript.

Conflict of interest:

The authors declare no conflict of interest related to this study.

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Table 1. Demographics of study population (N = 379)

Characteristics		N (%) or Median (range)
Age	Median (range)	59 (20-95)
	-29	23 (6.1%)
	30-39	33 (8.7%)
	40-49	53 (14.0%)
	50-59	81 (21.4%)
	60-69	64 (16.9%)
	70-	125 (33.0%)
Sex	Female	124 (32.7%)
	Male	255 (67.3%)
Number of PCR tests	Median (range)	2 (1-26)
Number of PCR test performed	1	177 (46.7%)
	2	83 (21.9%)
	3	61 (16.1%))
	4+	58 (15.3%)
Order of test showing the maximum number of copies[*1]	1st test	129 (63.9%)
	2nd test	55 (27.2%)
	3rd+ test	18 (8.9%)
No. days from onset of illness to hospitalization	Median (range)	5 (0-34)
No. of days in hospital	Median (range)	6 (0-35)
Number of inpatients per wave	First wave	17 (4.5%)
	Second wave	132 (34.8%)
	Third wave	125 (33.0%)
	Fourth wave	105 (27.7%)
Outcome	Death	29 (7.7%)
	Transfer	105 (27.7%)
	Discharge from hospital	245 (64.6%)
ICU admission		139 (36.7%)

ICU admission period	Median (range)	8 (1-84)
Use of devices	Ventilator	99 (26.1%)
	Extracorporeal membrane oxygenation (ECMO)	11 (2.9%)
	High Flow Nasal Therapy	27 (7.1%)
SARS-CoV-2 variant	L452R	2 (0.5%)
	N501Y	72 (19.0%)
Pharmaceutical treatment	Favipiravir	68 (17.9%))
	Ciclesonide	19 (5.0%)
	Nafamostat mesylate	3 (0.8%)
	Tocilizumab	19 (5.0%)
	Remdesivir	163 (43.0%)
	Dexamethasone	189 (49.9%)
	Baricitinib	16 (4.2%)
	Others	26 (6.9%)
Underlying diseases and conditions	Any	224 (59.10%)
	0	128 (33.8%)
	1	90 (23.8%)
	2	82 (21.6%)
	3+	79 (20.8%)
	Hypertension	146 (38.5%)
	Diabetes mellitus	82 (21.6%)
	Dyslipidemia	70 (18.5%)
	Hyperuricemia	29 (7.7%)
	Rheumatoid arthritis	8 (2.1%)
	Cancer	71 (18.7%)
	Chronic kidney disease	25 (6.6%)
	Stroke	19 (5.0%)
	Heart disease[*2]	34 (9.0%)

	Lung disease[*3]	41 (10.8%)
	Allergy	68 (17.94%)
	Pregnancy	7 (1.85%)
Smoking status	Never	221 (58.3%)
	Current	56 (14.8%)
	Past	102 (26.9%)
Vaccination status	Not at all	378 (99.7%)
	Once	1 (0.26%)

*1: Patients with only one test were excluded.

*2: Heart disease includes myocardial infarction, chronic heart failure, or atrial fibrillation.

*3: Lung disease includes asthma, chronic obstructive pulmonary disease.

Table 2. Crude and adjusted regression analysis of the association between patient characteristics and log-transformed copy number.

		Crude		Model 1[a]	
		coefficient	95% CI	coefficient	95% CI
Age	-29	ref.		ref.	
	30-39	0.98	-1.34 to 3.31	1.01	-1.26 to 3.29
	40-49	-0.24	-2.38 to 1.89	-0.77	-2.89 to 1.36
	50-59	0.12	-1.91 to 2.14	-0.52	-2.54 to 1.49
	60-69	0.59	-1.49 to 2.67	-0.22	-2.31 to 1.87
	70-	0.97	-0.98 to 2.91	-0.002	-1.96 to 1.96
Sex	Female	ref.		ref.	
	Male	0.65	-0.28 to 1.59	0.63	-0.38 to 1.63
Presence of underlying disease and conditions	Any (ref: none)	0.88	-0.01 to 1.77		
Number of underlying disease and conditions	0	ref.		ref.	
	1	-0.53	-1.68 to 0.63	-0.50	-1.75 to 0.75
	2	0.12	-1.07 to 1.31	0.07	-1.27 to 1.40
	3+	**1.94**	**0.74 to 3.14**	**1.83**	**0.45 to 3.20**
Specific underlying disease and conditions	Hypertension	0.60	-0.30 to 1.50		
	Diabetes mellitus	**1.55**	**0.49 to 2.60**	**1.25**	**0.16 to 2.35**
	Dyslipidemia	0.76	-0.37 to 1.89		
	Hyperuricemia	0.49	-1.17 to 2.14		
	Rheumatoid arthritis	**3.34**	**0.30 to 6.38**	**3.22**	**0.14 to 6.31**
	Cancer	0.20	-0.93 to 1.32		
	Chronic kidney	**1.98**	**0.22 to 3.74**	1.32	-0.48 to 3.11

	disease				
	Stroke	**3.11**	**1.12 to 5.10**	**2.37**	**0.34 to 4.41**
	Heart disease	0.52	-1.02 to 2.06		
	Lung disease	0.34	-1.08 to 1.75		
	Allergy	-0.40	-1.55 to 0.74		
	Pregnancy	0.95	-2.32 to 4.21		
Smoking Status					
	Never	ref.		ref.	
	Current	0.44	-0.84 to 1.72	0.32	-0.97 to 1.61
	Past	0.49	-0.54 to 1.51	0.38	-0.69 to 1.45

Bold indicates $p < 0.05$

Regression coefficient and 95 % C.I. are shown.

[a]Adjusted for gender, age, and smoking status.